REMARKS

Introductory Comments

Claims 23-34 were examined in the Office Action under reply and were rejected under 35 U.S.C. §112, first paragraph, as nonenabled, as well as under the judicially created doctrine of obviousness-type double patenting. These grounds of rejection are believed to be overcome by this response and are otherwise traversed for reasons discussed in detail below.

Overview of the Above Amendments

New claims 35 and 36 have been added. These claims depend from claims 23 and 29, respectively, and recite that the AAV virions are delivered intravenously. Support for the new claims can be found throughout the application at, e.g., page 40, lines 14-15.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

The Objection to Claims 24 and 30:

The Office objected to the use of the term "intraarterial" in claims 24 and 30, arguing that the word was "not disclosed anywhere in the instant specification." Office Action, page 3. However, applicant respectfully submits that one of skill in the art would understand applicant's description of delivery into the bloodstream to encompass intraarterial as well as intravenous administration. In particular, it is evident that the term "intravenous" is used broadly in the specification to denote any conventional mode of delivery into the bloodstream including, for example, intraarterial administration. As explained in paragraph 4 of the accompanying Declaration of Edward T. Wei, Ph.D., it is his opinion "that the application covers delivery of rAAV virions into the bloodstream." Additionally, Dr. Wei states in paragraph 4 of his Declaration that he understands delivery into the bloodstream "to encompass any of the various routes of delivery including intraarterial and intravenous administration." Moreover, Dr. Wei states in paragraph 4 that he views "intravenous administration of rAAV virions into the bloodstream as equivalent to intraarterial administration of rAAV virions into the bloodstream."

Accordingly, it is evident that one of skill in the art would construe the application to cover intraarterial delivery into the bloodstream. Thus, applicant submits that the basis for the term "intraarterial" is indeed apparent as required by MPEP 608.01(o). Thus, this objection is believed to be overcome and withdrawal thereof is respectfully requested.

The Double Patenting Rejection:

Claims 23, 25-29 and 31-34 were rejected under the judicially created doctrine of obviousness-type double patenting, over claims of U.S. Patent No. 6,211,163. Applicant notes the Examiner failed to specify which claims of the '163 patent are relied upon for the rejection. Nevertheless, in an effort to advance prosecution, applicant is

submitting a Terminal Disclaimer in compliance with 37 C.F.R. 1.321(c). Thus, this basis for rejection has been overcome. Withdrawal thereof is respectfully requested.

The Rejections Under 35 U.S.C. §112, First Paragraph:

In the interview, the Examiner requested applicant address the broad applicability of the present invention. In order to evidence this, applicant is submitting a number of references with the accompanying Supplemental Information Disclosure Statement. These references pertain to the delivery of rAAV virions including a wide range of gene sequences via a variety of methods to the bloodstream. For example, the references detailed herein describe delivery via the femoral and carotid arteries, as well as intracoronary and percutaneous intraarterial administration.

More particularly, Greelish et al., *Nat Med* (1999) 5:439-443 describes the infusion of histamine, as well as rAAV virions containing the human δ-sarcoglycan gene into the femoral artery of cardiomyopathic hamsters, a naturally occurring model for limb-girdle muscular dystrophy caused by a primary deficiency of δ-sarcoglycan. Delivery of the rAAV virions via the femoral artery resulted in efficient gene transduction with rescue of the sarcoglycan complex in muscle fibers of the distal hindlimb of the hamsters.

Svensson et al., *Circulation* (1999) 99:201-205 describes the introduction of rAAV virions containing the LacZ gene into mouse cardiomyocytes via intracoronary infusions. Stable β-galactosidase expression was observed in cardiomyocytes up to eight weeks after infusion.

Rolling F. et al., *Gene Ther* (1997) 4:757-761 describes infusion of rAAV virions containing the LacZ gene into rat carotid arteries by means of a Silastic catheter. Animals were sacrificed after various time points and the carotid arteries stained for β-gal activity. High levels of *in vivo* β-gal expression persisted for at least 30 days after gene transfer.

Kaplitt et al., *Ann Thorac Surg* (1996) 62:1669-76 describes delivery of rAAV virions containing a reporter gene into pig hearts via percutaneous intraarterial

infusion into the coronary vasculature using routine catheterization techniques. The presence of the reporter gene was detected up to six months after AAV-transduction of porcine myocardium.

Mimuro et al., *Abstracts of Scientific Presentations: The Fourth Annual Meeting of the American Society of Gene Therapy* (2001), abstract 743 describes a study using plasminogen activator inhibitor I (PAI-1) promoter-based AAV vectors to express thrombomodulin (TM) in vascular endothelial cells. The rAAV vectors were injected into the carotid artery of Mongolian gerbils. TM expression in the brain endothelial cells was detected.

Additionally, applicant is submitting the Declaration of Linda B. Couto, Ph.D. which describes successful intraarterial delivery of rAAV virions to rats and dogs. As explained in paragraph 4 therein, nude rats were infused with AAV virions containing the human Factor IX (hF.IX) gene via the tail vein, the portal vein, and the hepatic artery. Serum levels of circulating hF.IX protein were equivalent between the portal vein and hepatic artery routes of administration and only slightly lower with the tail vein. Similarly, adult dogs were injected with AAV virions via the hepatic artery. At least two lobes were transduced by AAV virions in every dog, while all four liver lobes were transduced in two of the dogs. See, paragraph 5 of Dr. Couto's Declaration. Based on these studies, it is Dr. Couto's opinion "that AAV virions can be successfully administered via the intra-arterial route and that results obtained therewith are similar, if not identical, to results obtained from intravenous administration of AAV virions." See, paragraph 6 of Dr. Couto's Declaration.

The above post-filing references, as well as the Couto Declaration, describe expression of several different proteins using rAAV virions, delivered by a variety of routes. It is therefore evident that the present invention is broadly applicable.

Applicant now turns to the specific rejections stated in the Office Action. Claims 23-34 were rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or

use the invention." Office Action, pages 3-4, bridging paragraph. The Examiner notes the specification discloses methods of administering rAAV virions into the bloodstream of a mammalian subject and methods of expressing a therapeutically effective amount of a protein by delivering rAAV virions to the bloodstream but cites a number of post-filing references in support of her rejection. Applicant respectfully submits that the present claims are indeed fully enabled.

In particular, as discussed with the Examiner in the interview, applicant is providing a copy of the Declaration of Gregory M. Podsakoff submitted in related Application Serial No. 09/309,042 (now U.S. Patent No. 6,211,163), evidencing the wide applicability of the present methods to a number of proteins. Moreover, applicant provides below a discussion of the post-filing references relied upon by the Examiner in making the present rejection. These references will be discussed in turn.

First, the Examiner contends that Kessler et al., appended as Exhibit B to the Podsakoff Declaration, shows that intramuscular injection of rAAV-hEPO results in substantially higher levels of circulating hEPO than intravenous administration and, further, that there is no correlation between hEPO expression and observed increases in hematocrit level "with any therapeutic effect on any blood disorder." Office Action, page 5. However, applicant submits that the reference indeed shows the utility of intravenous injection of rAAV virions comprising the hEPO gene. It is irrelevant that intramuscular injection appears to provide a greater effect than intravenous injection. 35 U.S.C. §112, first paragraph does not require that the claimed method be better than others. Rather, all that is required to satisfy the utility requirement of 35 U.S.C. §112, first paragraph (the apparent basis for this rejection) is that one of skill in the art would find the asserted utility specific, substantial and credible. See, the PTO Examination Guidelines on Utility Requirement.

Additionally, there is an art-recognized causal correlation between increasing hematocrit and therapeutic benefit *per se*. The Examiner's attention is directed to the appended abstracts to Collins et al. and Moreno et al. As explained in the Collins et al. abstract, hematocrits in the range of 33 to 36% appear to be associated with a 7%

reduced risk of death and hospitalizations compared with hematocrits of 30% to less than 33%. Furthermore, hematocrits less than 30% are associated with an 18% to 40% increased associated risk of death and hospitalizations. As set forth in the Moreno et al. abstract, increasing patient hematocrits using epoetin has a beneficial effect on quality of life. Accordingly, contrary to the Examiner's assertions, increases in hematocrit can indeed lead to significant therapeutic effects.

The Examiner also comments on Watson et al., appended to Dr. Podsakoff's Declaration as Exhibit C. In particular, the Examiner notes the publication shows that expression of GUS under the control of the CMV promoter in mice with the lysosomal disease, MPS, results in expression of GUS in liver, heart and muscles. Additionally, storage vacuoles in the liver are reduced due to GUS expression. However, the Examiner argues "lysosomal storage syndromes affect every cell in the body, and the expression of GUS in one or two organs is insufficient to treat the disease." Office Action, page 5. Applicant respectfully disagrees.

Contrary to the Examiner's assertions, Watson et al. clearly shows a therapeutic benefit to animals administered rAAV-GUS intravenously – namely – healthier livers. Not only were gycosaminoglycan levels in the liver reduced to normal amounts, storage granules were also reduced dramatically. Thus, the disease phenotype was reversed in the liver. Applicant's claims do not require a complete cure. Rather, the claims are directed to methods of administering rAAV virions into the bloodstream to obtain a therapeutic effect (claims 23-29 and 35) and methods of expressing therapeutically effective amounts of a protein in a mammalian subject to provide for a therapeutic effect (claims 30-34 and 36). Surely, the Examiner cannot refute that applicant has shown a very significant, casual therapeutic benefit of rAAV virion-mediated GUS delivery. Thus, the evidence presented in Watson et al. is believed to be directly relevant to the question of efficacy vis-a-vis the present claims.

The Examiner also cites Brockstedt et al. attached to the Podsakoff Declaration as Exhibit D. The Examiner notes this reference demonstrates that intravenous injection of rAAV-OVA results in OVA-specific CTL and antibodies

sufficient to reduce OVA-expressing tumor growth in mice. However, at page 5 of the Office Action, the Examiner argues "the skilled artisan would not consider the challenge of mice with an OVA expressing tumor as a model for cancer as ovalbumin is highly immunogenic protein that is not a naturally occurring tumor antigen." On page 8 of the Office Action, the Examiner states: "At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms...." These arguments ignore the recitations in the claims. Brockstedt et al. demonstrates that rAAV virions effectively present antigens to the immune system in such a way that an immune response may be generated. Applicant does not dispute that OVA is not a naturally occurring tumor antigen. However, OVA is traditionally used to explore immune responses in various systems. One of skill in the art would certainly find these results indicative of the ability of rAAV virions to deliver antigens to confer a therapeutic benefit and consider such an allegation of utility credible. The claims are not limited to treatment of cancer. One could easily envision other therapeutic benefits that might occur by delivery of antigens in such a way that humoral and/or cell-mediated immunity results.

Finally, with respect to Nakai et al., attached to Dr. Podsakoff's Declaration as Exhibit E, the Examiner acknowledges that rAAV virion-mediated intravenous delivery of the gene encoding human Factor IX under the control of the EF1α promoter, resulted in expression of Factor IX in the liver and concentrations of Factor IX in the serum which correlate to a therapeutic effect. The Examiner argues, however, that delivery of the Factor IX gene under the control of a CMV promoter failed to achieve detectable levels of Factor IX. However, it is well known that the CMV promoter performs poorly in the liver. See, e.g., Guo et al., *Gene Ther.* (1996) 3:802-810 (Abstract) and Najjar et al., *Gene* (1999) 230:41-45 (Abstract), attached hereto for the Examiner's convenience. The results reported in Nakai et al. are consistent therefore with art-known facts about the CMV promoter.

Based on the foregoing, applicant submits that Dr. Podsakoff's Declaration is highly probative of the broad applicability of the use of rAAV virions for delivering a wide variety of genes to the bloodstream to confer a therapeutic effect.

The Examiner further argues that the specification "does not provide an enabling disclosure for achieving therapeutic levels of expression of any protein capable of treating any disease or condition by administration of an rAAV which utilizes any promoter to express the therapeutic gene of interest by any method of delivery to the bloodstream." Office Action, page 6. The Examiner supports this contention by alleging that Watson et al. showed expression of GUS in a limited number of tissues and that the "specification does not provide sufficient guidance as to the identity of promoters capable of producing therapeutic levels of gene expression in any and all types of cells...Whereas Watson et al. observed GUS gene expression in liver cells infected with rAAV encoding GUS operatively linked to a CMV promoter following intravenous rAAV injection, Nakai et al. failed to observe expression of Factor IX in liver cells following intravenous injection of a similar rAAV encoding Factor IX operatively linked to CMV." Office Action, page 7.

However, Watson et al. did not compare expression levels of GUS using other promoters with levels achieved using CMV. It is entirely possible that had Watson et al. expressed the GUS gene using a more "liver-friendly" promoter, higher expression levels would have been achieved. Accordingly, no comparisons between Watson et al. and Nakai et al. may be made.

Moreover, applicant submits that one of skill in the art could readily identify proper promoters to use for specific applications, using a routine amount of experimentation. A wide variety of promoters, as well as their tissue specificity, was known at the time the application was filed. Accordingly, one of skill in the art could determine appropriate promoters to use for a given target tissue, without undue experimentation. Moreover, the independent claims recite that the expression control elements "provide for transcription and translation of the selected gene in a desired host cell *in vivo*." Accordingly, this functional limitation assures that the promoter used will be functional in the specific host tissue targeted.

The Examiner also states that at the time of filing, *in vivo* gene therapy techniques were considered to be highly unpredictable. Office Action, page 7. A

collection of general reviews of gene therapy have been used by the Office to support this assertion. However, these references fail to address the salient issue here, that is, whether applicant has enabled methods for delivering rAAV virions encoding a therapeutic protein to the bloodstream, to result in a therapeutic effect. Applicant disagrees with the Office's assessment for the following reasons

Applicant's charge under 35 U.S.C. §112, first paragraph, is to provide a specification which teaches one of ordinary skill in the art how to make and use the claimed invention without "undue experimentation," as judged by the standards of those skilled in the art. Applicant has met this charge. Specifically, as acknowledged by the Examiner on page 4 of the Office Action, applicant's specification describes methods for delivering a gene to the bloodstream to obtain a therapeutic benefit using rAAV virions. Moreover, applicant has supplied additional evidence showing the applicability of the claimed methods to the delivery of wholly unrelated substances (see, Dr. Podsakoff's Declaration). Particularly, Dr. Podsakoff's Declaration shows that the claimed methods are broadly applicable to a wide variety of genes. The Declaration describes expression of EPO in blood following intravenous delivery of rAAV virions encoding EPO, with a concomitant rise in hematocrit levels (paragraph 4 of the Declaration); the sustained expression of GUS following intravenous delivery to cause a reversal of liver damage characteristically present in MPS disorders (paragraph 5 of the Declaration); the presentation of an antigen to the immune system to cause both humoral and cell-mediated immune responses (paragraph 6 of the Declaration); and the sustained stable expression of Factor IX at therapeutic levels in liver following portal vein administration of rAAV virions encoding Factor IX (paragraph 7 of the Declaration). Certainly, applicant has presented ample evidence to enable the methods as claimed.

Based on the foregoing, applicant submits that more than adequate evidence of enablement has been provided. Accordingly, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

In view of the foregoing, applicant submits that the claims are now in condition for allowance and request early notification to that effect. If the Examiner notes any further matters which she believes may be resolved by a telephone interview, she is encouraged to contact Christina Thomson by telephone at (510)748-7208, or by fax at (510)748-7368.

Respectfully submitted,

Date: 11/26/01

By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & PASTERNAK LLP
90 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 325-7812
Fax: (650) 325-7823

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

New claims 35 and 36 have been added:

--35. (New) The method of claim 23, wherein the AAV virions are delivered intravenously.

36. (New) The method of claim 29, wherein the AAV virions are delivered intravenously.--

CURRENTLY PENDING CLAIMS

23. A method of administering recombinant adeno-associated virus (AAV) virions into the bloodstream of a mammalian subject, said method comprising:

(a) providing AAV virions comprising a selected gene operably linked to expression control elements that provide for transcription and translation of the selected gene in a desired host cell *in vivo*; and

(b) delivering said recombinant AAV virions to the bloodstream, whereby said selected gene is expressed at a level which provides a therapeutic effect in the mammalian subject.

24. The method of claim 23, wherein the AAV virions are delivered intraarterially.

25. The method of claim 23, wherein the selected gene encodes a therapeutic protein useful for treating a blood disorder.

26. The method of claim 25, wherein the therapeutic protein is erythropoietin.

27. The method of claim 25, wherein the blood disorder is hemophilia.

28. The method of claim 23 wherein said protein is secreted.

29. A method of expressing a therapeutically effective amount of a protein in a mammalian subject, said method comprising:

administering into the bloodstream of said subject a pharmaceutical composition which comprises (a) a pharmaceutically acceptable excipient; and (b) recombinant AAV virions comprising a selected gene operably linked to expression

control elements that provide for transcription and translation of the selected gene in a desired host cell *in vivo*, whereby said virions transduce cells in said subject, and said selected gene is expressed by the transduced cells at a level which provides for a therapeutic effect in said subject.

30. The method of claim 29, wherein the pharmaceutical composition is delivered intraarterially.

31. The method of claim 29, wherein the selected gene encodes a therapeutic protein useful for treating a blood disorder.

32. The method of claim 31, wherein the therapeutic protein is erythropoietin.

33. The method of claim 31, wherein the blood disorder is hemophilia.

34. The method of claim 29 wherein said protein is secreted.

35. (New) The method of claim 23, wherein the AAV virions are delivered intravenously.

36. (New) The method of claim 29, wherein the AAV virions are delivered intravenously.